General

Guideline Title

Clinical utility of multigene profiling assays in invasive early-stage breast cancer.

Bibliographic Source(s)

Chang MC, Souter LH, Kamel-Reid S, Rutherford M, Bedard P, Trudeau M, Hart J, Eisen A, Molecular Oncology Advisory Committee. Clinical utility of multigene profiling assays in invasive early-stage breast cancer. Toronto (ON): Cancer Care Ontario (CCO); 2016 Jun 8. 54 p. (Program in Evidence-Based Care Recommendation Report; no. MOAC-4). [81 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for level of evidence (IA, IB, II, III, IV) and strength of recommendation (Moderate, Weak) are provided at the end of the Major Recommendations field.

Recommendation Preamble

Multigene profiling assays are used in combination with clinical-pathological factors in invasive breast cancer patients to ascertain whether a patient's estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative tumour has an intrinsic high-risk or low-risk profile. Oncotype DX, Prosigna, and EndoPredict are examples of assays that are commercially available in Ontario. Although no assay represents a gold standard, Oncotype DX is supported by the widest range of evidence for prognosis and prediction of chemotherapy benefit, while both Prosigna and EndoPredict have evidence-based validity in providing some of the same or similar clinical information. Figure 1-1 in the original guideline document graphically summarizes the included recommendations in a decision tree format for clinical use. At the time of publication, Oncotype DX is the only assay that is publically funded in Ontario.

Research Questions

Given that there are now multiple multigene assays that can predict for recurrence in patients with invasive breast cancer, what is the level of evidence supporting the clinical validity and utility for each of these assays?

- Given that Oncotype DX is part of standard practice in Ontario, what is the evidence that other assays can complement or replace Oncotype DX for certain clinical utilities?

Recommendation 1

Clinicians may offer multigene profile assay testing to potential chemotherapy candidates with invasive breast carcinoma that is ER-positive/HER2-negative (Recommendation Type: Evidence-based; Evidence Quality: Level IB; Recommendation Strength: Moderate).

Recommendation 2

In patients with node-negative ER-positive/HER2-negative disease, clinicians may use a low-risk result from Oncotype DX, Prosigna, or EndoPredict/EPclin assays to support a decision to withhold chemotherapy (Recommendation Type: Evidence-based; Evidence Quality: Level IB; Recommendation Strength: Moderate).

Recommendation 3

In patients with node-negative ER-positive/HER2-negative disease, clinicians may use a high-risk result from Oncotype DX to support a decision to offer chemotherapy. A high-risk Oncotype DX result in this subpopulation has been associated with both poor prognosis without chemotherapy, and a prediction of benefit from giving chemotherapy (Recommendation Type: Evidence-based; Evidence Quality: Level IB-II; Recommendation Strength: Weak).

Recommendation 4

In some patients with ER-positive/HER2-negative tumours and 1 to 3 nodes involved (N1a disease), clinicians may withhold chemotherapy based on a low-risk Oncotype DX or Prosigna score if the decision is supported by other clinical, pathological, or patient-related factors (Recommendation Type: Consensus-based; Evidence Quality: Level II; Recommendation Strength: Weak).

Recommendation 5

In patients with ER-positive disease, there is insufficient evidence to recommend the use of multigene profiling assays to inform clinical decision making for late risk of recurrence. A high-risk score using Prosigna or EndoPredict prognosticates for late recurrence; however, evidence is lacking that these tests predict for benefit of extended adjuvant endocrine treatment beyond five years. (Recommendation Type: Consensus-based; Evidence Quality: Lack of evidence; Recommendation Strength: Weak).

Definitions

Summary of Study Categories as Defined by the Tumour Marker Utility Grading System

Study Category	Elements of Study
A	Randomised controlled trial (RCT) designed with tumour biomarker/assay as the intervention
B	RCT designed to address a treatment intervention that is not the tumour biomarker/assay. Study prospectively enrolls and follows patients, and collects tumour samples, and then uses archived tumour tissue retrospectively to evaluate the tumour biomarker/assay.
C	Prospective observational registry study that prospectively enrolls patients in a registry and collects, processes, and archives tumour specimens, but treatment and follow-up are standard of care. Archived tumour tissue is used retrospectively to evaluate the tumour biomarker/assay.
D	Retrospective studies

Levels of Evidence based on the Tumour Marker Utility Grading System

Level of Evidence	Number and Types of Studies
IA	1 category A study
IB	At least 2 category B studies with consistent results
II	1 category B study, OR multiple category B studies with inconsistent results, OR at least 2 category C studies with consistent results
III	1 category C study OR multiple category C studies with inconsistent results
IV	Any number of category D studies. Note that Level IV evidence is not sufficient for determining clinical utility.

Strength of Recommendations

The rating scheme for the strength of recommendations is specific to this particular guideline because the subject is one that has not been studied much methodologically (e.g., recommendations on molecular tests). The rule was that if there was level I evidence (according to the scheme laid out by Simon et al.) it was a moderate-strength recommendation, and otherwise it was weak. Given the nature of topic and the type of evidence involved, the authors believed that strong recommendations were for the most part impossible.

Clinical Algorithm(s)

An algorithm titled "Multigene Profiling Assay Decision Tree" is provided in the original guideline document.

Scope

Disease/Condition(s)

Early-stage breast cancer

Guideline Category

Diagnosis

Evaluation

Risk Assessment

Technology Assessment

Clinical Specialty

Internal Medicine

Medical Genetics

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To determine the level of evidence supporting the clinical validity and utility for the profiling assays in question
- To determine whether certain breast cancer patient populations in Ontario would benefit from alternative tests (in addition to Oncotype DX)

Target Population

Women diagnosed with invasive early-stage breast cancer for whom further information is needed for treatment decision making

Interventions and Practices Considered

1. Multigene profile assay testing
2. Decisions to withhold or provide chemotherapy based on assay results

Major Outcomes Considered

- Prognostic and predictive value of assays
- Risk of recurrence (local and distant) at 5 and 10 years
- Overall survival (OS)
- Disease-free survival (DFS) or relapse-free survival (RFS)
- Change in chemotherapy treatment plan

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. Systematic reviews published as a component of practice guidelines were also considered eligible for inclusion. An electronic search employing OVID was used to systematically search the MEDLINE and EMBASE databases for systematic reviews evaluating the clinical utility of Oncotype DX, MammaPrint, Prosigna/PAM50, and EndoPredict. OVID was searched from 2002 to week 31 of 2015 using the following keywords: "oncotype", "21 gene", "recurrence score", "prosigna", "pam50", "mammaprint", "70 gene", and "endopredict". In addition, Web sites/databases of specific guideline developers that used systematic review as their evidentiary base, as well as systematic review producers, were also searched, using the same keywords and for the same time period. These Web sites/databases included: the National Institute for Health and Care Excellence (NICE), American Society of Clinical Oncology (ASCO), and the Cochrane Database of Systematic Reviews.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool to determine whether existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence base.

Search for Primary Literature

Below are methods for locating and evaluating primary literature if no existing systematic reviews were identified, or if identified reviews were incomplete in some fashion. If the identified systematic reviews are incomplete, then the primary literature review might be reduced in scope (e.g., subject areas covered, time frames covered).

Literature Search Strategy

OVID was used to systematically search the MEDLINE and EMBASE databases for articles evaluating the clinical utility of multigene profiling assays, published between 2002 and week 7 of 2016. The literature search strategy included keywords for identification of the multigene assays of interest, as well as keywords to identify important clinical utility and clinical validation studies that were known a priori. The complete literature search strategy can be found in Appendix 2 in the original guideline document. In addition to the MEDLINE and EMBASE databases searches, reference lists of included systematic reviews and primary literature were scanned for potentially useful studies.

Study Selection Criteria and Process

Identified studies that used prospectively enrolled patients and prospectively collected tumour specimens were considered for inclusion in the evidentiary base of this systematic review. Retrospective cohort studies, case-control studies, case series, letters, editorials, and studies not published in English were excluded from the evidentiary base. The literature search flow diagram can be found in Appendix 3 in the original guideline document.

All hits from the OVID literature search were input into reference management software (EndNote X6), where duplicate citations were removed. A review of the titles and abstracts that resulted from the search was performed by one reviewer and verified by a second. For those items that warranted full-text review, one reviewer determined whether the inclusion and exclusion criteria were met. The list of proposed studies was verified by the Working Group.

Number of Source Documents

Results

Search for Existing Systematic Reviews

The search for existing systematic reviews identified five publications that were considered for inclusion after full-text review. Although all of the identified reviews evaluated the clinical utility of one or more multigene profiling assays, none fully addressed the objectives of the systematic review. Since the literature base in this field is small and the reviewers sought to assess the primary literature based on the level of evidence (LoE) framework, none of the identified systematic reviews were incorporated.

Search for Primary Literature

Twenty-four studies were identified that met the inclusion criteria (see Appendix 3 in the original guideline document). Seventeen studies focused on the clinical utility of the multigene profiling assays and seven studies focused on a change in treatment plan. Table 3-1 in the original guideline document summarizes the number of studies that evaluated the prognostic and predictive value of each assay, stratified by the level of evidence for those studies. Table 3-2 in the original guideline document summarizes the number of studies that assessed a change in chemotherapy treatment based on the results of an assay.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

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	the tumour biomarker/assay.
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Levels of Evidence based on the Tumour Marker Utility Grading System

Level of Evidence	Number and Types of Studies
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IV	Any number of category D studies. Note that Level IV evidence is not sufficient for determining clinical utility.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Assessment of Study Quality and Potential for Bias

Data were extracted from all studies that passed full-text review by one reviewer. Ratios, including hazard ratios, were expressed with a ratio <1.0 indicating reduced risk for recurrence or death, unless otherwise indicated. All extracted data and information were audited by an independent auditor.

A framework to evaluate the clinical utility of tumour markers was proposed by Hayes et al. in 1996. This tumour marker utility grading system was further refined in 2009 and will be used to grade the levels of evidence of the prognostic and predictive studies included in this review. The framework assigns a study type category based on five elements: 1) clinical trial design; 2) patients and patient data; 3) specimen collection, processing, and archival; 4) statistical design and analysis; and 5) study validation. A level of evidence (LoE) is then determined for the entire body of evidence based on the number of each study category type identified. (See the "Rating Scheme for the Strength of the Evidence" field.)

In brief, category A studies are randomized controlled trials (RCTs) designed with the tumour marker as the intervention, and only one RCT is required for LoE I. Level IB evidence is obtained with at least two category B study with consistent results. Category B studies are defined as RCTs that were designed to address a treatment intervention that is not the tumour marker and that prospectively enroll and follow patients, and prospectively collect tumour specimens, but the archived tumour tissue is used retrospectively to evaluate the tumour marker. Level II evidence is obtained when there is only one category B study, or multiple category B studies with inconsistent results, or when at least two category C studies with consistent results are identified. Category C studies are prospective observational registry studies that prospectively enroll patients in a registry and must prospectively collect, process, and archive tumour specimens, but treatment and follow-up are standard of care. Level III evidence is obtained when only one category C study is available, or if more than one is identified, but results are not consistent. Finally, level IV evidence is obtained when only retrospective observational studies are identified. Retrospective (category D) studies that assessed the prognostic or predictive abilities of the multigene profiling assays were excluded *a priori*; however, retrospective studies that evaluated a change in chemotherapy regimen based on the findings of a multigene profiling assay were included. In addition to quality assessment based on the tumour marker grading system, sources of bias, country in which the study was conducted, and sources of funding were extracted and considered to determine the overall quality of the studies.

Synthesizing the Evidence

Due to the anticipated variation in outcomes measured, a meta-analysis was not planned.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Recommendation Report Developers

At the request of Molecular Oncology Advisory Committee (MOAC), this recommendation report was developed by a Working Group consisting of a geneticist, two pathologists, three medical oncologists, the manager of pathology and laboratory medicine program at Cancer Care Ontario (CCO), and a health research methodologist.

The Working Group was responsible for reviewing the evidence base, drafting the recommendations, and responding to comments received during the document review process.

Recommendation Report Development Methods

The Program in Evidence-Based Care (PEBC) produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle. For Recommendation Reports, this process includes a systematic review, interpretation of the evidence and recommendation drafting by the Working Group, internal review by a methodology expert, and final approval by the Sponsoring Committee.

The PEBC uses the Appraisal of Guidelines Research and Evaluation (AGREE) II framework as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

Research Questions

Given that there are now multiple multigene assays that can predict for recurrence in patients with invasive breast cancer, what is the level of evidence supporting the clinical validity and utility for each of these assays?

- Given that Oncotype DX is part of standard practice in Ontario, what is the evidence that other assays can complement or replace Oncotype DX for certain clinical utilities?

PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook (see the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

The rating scheme for the strength of recommendations is specific to this particular guideline because the subject is one that has not been studied much methodologically (e.g., recommendations on molecular tests). The rule was that if there was level I evidence (according to the scheme laid out by Simon et al.) it was a moderate-strength recommendation, and otherwise it was weak. Given the nature of topic and the type of evidence involved, the authors believed that strong recommendations were for the most part impossible.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Recommendation Report Review and Approval

Internal Review

The recommendation report was reviewed by the Director of the Program in Evidence-Based Care (PEBC). The Working Group is responsible for ensuring the necessary changes are made. If those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

Report Approval by Molecular Oncology Advisory Committee (MOAC)

After internal review, the report was presented to the MOAC. The MOAC reviewed the document in e-mail format in May 2016, and formally approved the document over teleconference on May 24, 2016.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The supporting evidence is identified and graded for each recommendation (see the "major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Multigene profiling assays aid in risk stratifying early breast cancers. The basic objective of all of these tests is to separate tumours into a low-risk (i.e., low proliferation/invasiveness) and a high-risk group (i.e., high proliferation/invasiveness). Studies examining physician treatment decisions show that multigene profiling assays may change management in 22% to 52% of cases, depending on the level of confidence of the pre-assay recommendation.

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario (CCO) makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.
- See the original guideline document for qualifying statements related to each recommendation.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy is not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Chang MC, Souter LH, Kamel-Reid S, Rutherford M, Bedard P, Trudeau M, Hart J, Eisen A, Molecular Oncology Advisory Committee. Clinical utility of multigene profiling assays in invasive early-stage breast cancer. Toronto (ON): Cancer Care Ontario (CCO); 2016 Jun 8. 54 p. (Program in Evidence-Based Care Recommendation Report; no. MOAC-4). [81 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Jun 8

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario (CCO) supported by the Ontario Ministry of

Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Molecular Oncology Advisory Committee

Clinical Utility of Multigene Profiling Assays in Early-Stage Breast Cancer Working Group

Composition of Group That Authored the Guideline

Working Group Members: M.C. Chang, L.H. Souter, S. Kamel-Reid, M. Rutherford, P. Bedard, M. Trudeau, J. Hart, A. Eisen

Financial Disclosures/Conflicts of Interest

Conflict of interest declarations for all authors are summarized in Appendix 1 in the original guideline document, and were managed in accordance with the Program in Evidence-Based Care (PEBC) Conflict of Interest Policy.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Cancer Care Ontario (CCO) Web site.

Availability of Companion Documents

The following are available:

- Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available from the Cancer Care Ontario (CCO) Web site.
- Program in Evidence-based Care methods handbook. Toronto (ON): Cancer Care Ontario (CCO); 2014 Sep 23. Available from the Program in Evidence-based Care (PEBC) Toolkit Web site.
- Program in Evidence-based Care document assessment and review protocol. Toronto (ON): Cancer Care Ontario (CCO); 2015 Apr 16. 15 p. Available from the CCO Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 8, 2016.

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